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(54) Title: **AEROSOL FORMULATIONS OF Δ^8 TETRAHYDROCANNABINOL**

(57) Abstract: The application discloses an aerosol formulation comprising Δ^8 Tetrahydrocannabinol for use as a medicine, and the use of Δ^8 Tetrahydrocannabinol to treat a condition selected from pain, appetite loss, multiple sclerosis and asthma.

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AEROSOL FORMULATIONS OF Δ^8 TETRAHYDROCANNABINOL

Field of the Invention

The invention is directed to the therapeutic use of Δ^8 Tetrahydrocannabinol (Δ^8 THC). In particular, the invention provides Δ^8 THC formulations suitable for administration to the buccal or nasal mucosa or the pulmonary airways. Such Δ^8 THC formulations are useful for the reduction, elimination or prevention of pain associated with any medical condition; the stimulation of appetite; the reduction, elimination or prevention of nausea; the reduction, elimination or prevention of vomiting (antiemetic properties); the relaxation of muscle tissue (e.g., for the treatment of multiple sclerosis).

15 Summary of the Related Art

Currently there is much interest in the possible medical use of Cannabis or its natural constituents. In Great Britain, for example, two House of Lords reports from 1999 and 2001 have both recommended further investigation as to whether the anecdotal (i.e., not scientifically proved) reports from certain patients with multiple sclerosis and other long term painful or debilitating diseases have a genuine basis.

20 Cannabis use is centuries old, particularly in China and India, although the abuse (mostly in the West) is of more recent origin and dates back only about 100 years.

There have been many arguments as to the dangers of Cannabis and its addictive potential, however a general consensus seems to be growing that it is probably no worse than tobacco in terms of addiction although there is a potential for 25 longer term psychosis if large doses are taken for the immediate "high". The common method of taking Cannabis is smoking, but this gives rise to similar bad effects on the lung from tars and other components as for tobacco.

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Currently there are three approaches to the investigation of possible medical uses for cannabinoids (the name for the group of "active" molecules in *Cannabis*).

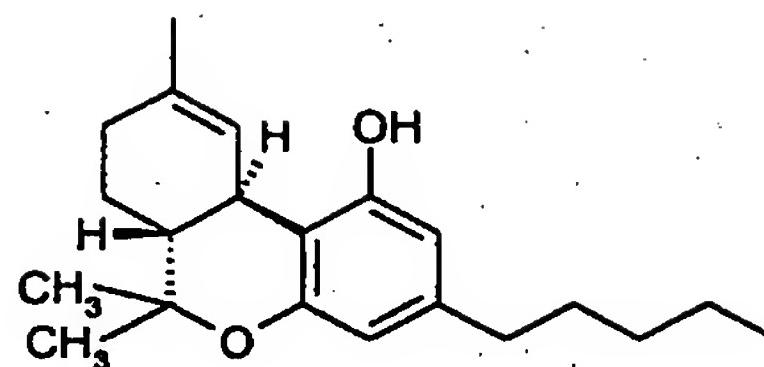
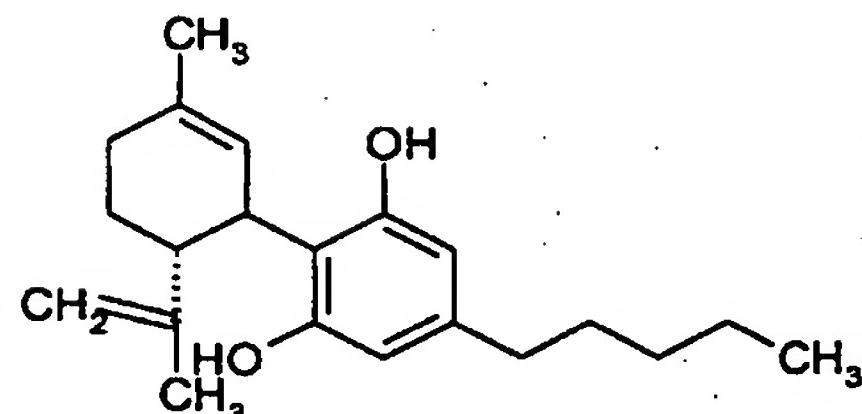
One is to try to standardize an extract from a plant or mixtures of plants. Much of the current work both in the UK and US is based on the use of a "Cannabis Oil" extracted from plants. This contains a mixture of natural molecules, some of which are at present not characterized. The extract must be standardized which is difficult to achieve even in rigorously controlled growing conditions and it is very difficult if not impossible to purify the active constituents away from plant materials such waxes, sterols etc.

The second is to try to develop new synthetic molecules based on the structures of the natural cannabinoids hopefully without some of the possible psychotropic side effects. The synthesis of new molecules is being investigated by a number of academic centers but is extremely costly to complete and bring to market. The generally accepted cost to carry out all the chemistry, pharmacology, clinical trials etc. to bring a new drug to market is usually quoted at about \$300 million and this by no means guarantees success.

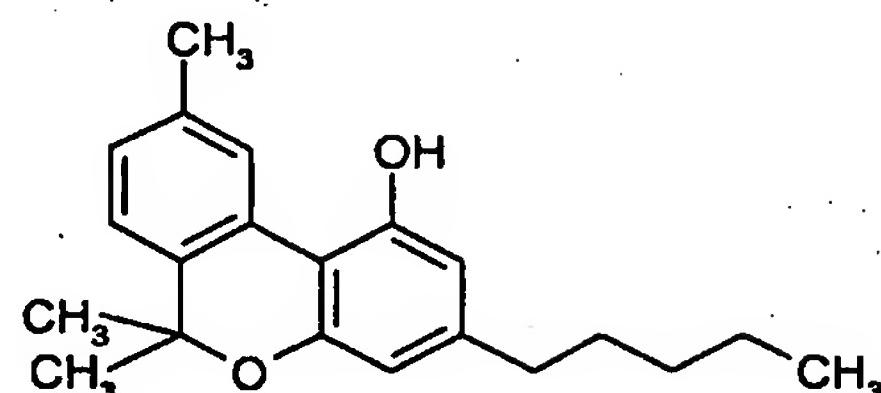
The third is to synthesize synthetic equivalents of some of the natural cannabinoid molecules. The main active constituent of *Cannabis* is now known to be THC (tetrahydrocannabinol) with two other major components Cannabidiol and Cannabinol depending on the plant used and the growing conditions.

There are then many other minor components some of which have been identified and some of which have not. These structures are shown below.

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 Δ^9 -tetrahydrocannabinol (Δ^9 -THC)

Cannabidiol



Cannabinol

5

A major problem associated with the medicinal use of cannabinoids entails the method for administering said cannabinoids. Smoking *Cannabis* leaves or resin for medical use would not be acceptable in many countries e.g., UK, as it is not standardized, difficult to control the dosage and would result in similar tars etc., depositing in the lung as from tobacco smoking.

There are some current trials using capsules of *Cannabis* extracts or its synthetic components but these are known to be less than desirable as cannabinoids are rapidly metabolised in the body when given orally into the stomach (so called "First Pass Metabolism") and large doses are needed to get possible active molecules into the blood stream in adequate amounts. This leaves large amounts of metabolites, some of which must have clinical activity of some sort and may well give rise to some of the unwanted side effects.

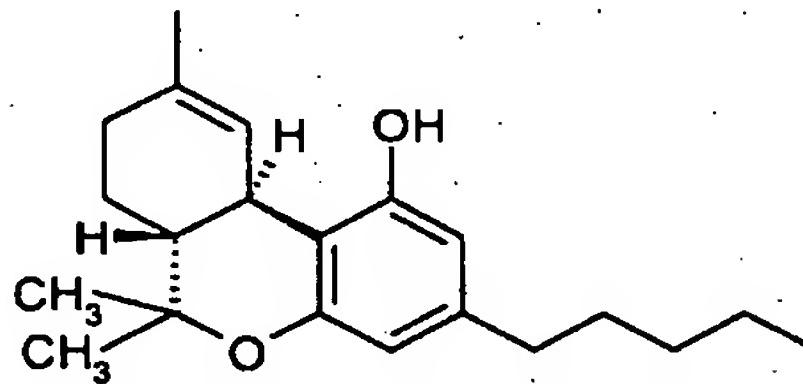
Others are using a standardized extract given under the tongue in the mouth where the active components are absorbed directly into the veins in the mouth so avoiding the "First Pass Metabolism", they use a specially formulated spray to dose the drug.

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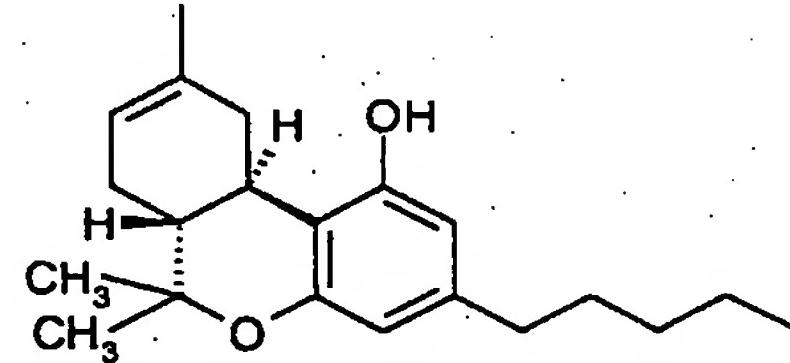
Still others have tried similar approaches. While mixtures of active molecules were produced, it was impossible to remove all the associated plant material, which was of a waxy nature. This would make them unsuitable for administration directly 5 into the lungs as the removal of waxy material from the lungs would be problematic and may well lead to a build up of wax in the lung with all the long term problems and dangers this may involve.

One possible approach to the problem entails the 10 possibility of using chemically synthesized molecules or mixtures of the naturally occurring cannabinoids. This is because there is some limited toxicity data already available on such compounds. For example, Abrahamov, et al., (*Life Sciences* 56: 2097-2102, 1995 and U.S. Patent No. 5,605,928) 15 have shown promising results using a synthetic version of the THC in children with cancer where the incidence of nausea was greatly reduced with no significant side effects.

This molecule is called Δ^8 THC in comparison the naturally occurring Δ^9 THC, which as mentioned earlier, is the main 20 naturally occurring active constituent of *Cannabis*. The structures are shown below and the two molecules can be seen to differ only by the position of a double bond from 8 to 9.



Δ^9 -tetrahydrocannabinol (Δ^9 -THC)



Δ^8 -tetrahydrocannabinol (Δ^8 -THC)

25 Δ^8 THC is reportedly easier to synthesize than Δ^9 THC. It exists as an oil at ambient temperature.

The literature has many anecdotal references to possible medicinal uses of *Cannabis*, for example: Relief of Pain (post operatively, Oncological, Phantom Limb etc), Multiple 30 Sclerosis, Anti-nausea, Appetite Stimulation, Asthma etc.

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Pain relief in terminal oncology is now widely accepted to be the main concern of the physician and the main component of this is morphine normally given as delayed release tablets (or by injection or infusion). In the terminal stages of the
5 disease, it often becomes difficult for the patient to swallow, either due to GI tract obstruction or an associated nausea caused by the disease or by some of the anti-cancer treatments, and so an aerosol treatment directly into the lungs might well be of significant value.

10 The present invention addresses such problems associated with medicinal cannabinoid administration by providing an aerosol formulation where the principle active medicament is Δ^8 Tetrahydrocannabinol.
15

SUMMARY OF THE INVENTION

The present invention provides aerosol formulations for the medicinal administration of Δ^8 Tetrahydrocannabinol. In a second aspect, the invention provides a method for treating patients to alleviate the symptoms associated with a number of
20 disease states using Δ^8 Tetrahydrocannabinol.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention provides Δ^8 Tetrahydrocannabinol formulations and methods for treating patients to alleviate the
25 symptoms associated with a number of disease states. Therefore, an object of the invention is (a) the reduction, elimination or prevention of pain associated with any medical condition; (b) the stimulation of appetite; (c) the reduction, elimination or prevention of nausea; (d) the reduction, elimination or prevention of vomiting (antimetic properties); (e) the relaxation of muscle tissue (e.g. for the treatment of multiple sclerosis).

30 The active medicament for these formulations and methods

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is Δ^8 Tetrahydrocannabinol (Δ^8 THC).

The present invention provides aerosol formulations for the medicinal administration of Δ^8 Tetrahydrocannabinol and novel medicinal uses of Δ^8 Tetrahydrocannabinol. The term Δ^8 Tetrahydrocannabinol (Δ^8 THC) designates Δ^8 Tetrahydrocannabinol and prodrugs (hereinafter collectively designated as " Δ^8 THC moieties").

According to one aspect, the present invention provides the use of Δ^8 Tetrahydrocannabinol in the manufacture of an aerosol formulation for medicinal administration to a patient from an aerosol delivery device.

According to an alternative aspect, the present invention provides a method of treating a mammal suffering from a condition indicating treatment with a Δ^8 Tetrahydrocannabinol, which comprises administering an aerosolized aerosol formulation containing a therapeutically effective amount of Δ^8 Tetrahydrocannabinol to the mammal.

The condition may be any medical condition indicating treatment with Δ^8 Tetrahydrocannabinol, for example a condition selected from pain, nausea, vomiting, appetite loss, multiple sclerosis and asthma.

In one embodiment of the invention, the patient (or mammal) may be a cancer patient undergoing chemotherapy, and the condition is selected from pain, nausea, vomiting and appetite loss.

Particular mention may be made of the case where the condition is pain associated with phantom limb syndrome.

Particular mention may also be made of the case where the condition is appetite loss associated with anorexia nervosa.

In one embodiment, the aerosol formulation is for administration to the lungs of the patient.

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In another embodiment, the aerosol formulation is for administration to the buccal or nasal mucosa of the patient.

The use of Δ^8 Tetrahydrocannabinol to treat pain, appetite loss, multiple sclerosis or asthma is believed to be
5 novel.

According to another aspect, therefore, the present invention provides the use of Δ^8 Tetrahydrocannabinol in the manufacture of a medicament for the treatment of a condition selected from pain, appetite loss, multiple sclerosis and
10 asthma.

In an alternative aspect, the present invention provides a method of treating a mammal suffering from a condition selected from pain, appetite loss, multiple sclerosis and asthma, which comprises administering a therapeutically effective amount of
15 Δ^8 Tetrahydrocannabinol to the mammal.

For the novel medical uses, the Δ^8 Tetrahydrocannabinol may be formulated in a formulation suitable for oral, inhalation (including via the nasal mucosa or directly the pulmonary tissues), rectal, ophthalmic, (including intravitreal or intracameral), nasal, topical (including buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous, intradermal and intratracheal) administration. In addition, the combinations may be formulated with polymers allowing for sustained release of the compound.
20 Preferably the Δ^8 Tetrahydrocannabinol is formulated as an aerosol formulation for administration using an aerosol delivery device.

According to another aspect, the present invention provides an aerosol delivery device containing an aerosol formulation comprising Δ^8 Tetrahydrocannabinol.
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According to yet another aspect, the present invention provides an aerosol formulation for use in an aerosol delivery device, which comprises Δ^8 Tetrahydrocannabinol.

Preferably, the aerosol formulation further comprises a propellant.

The propellant is preferably selected from 1,1,1,2-tetrafluoroethane (HFA 143a) and 1,1,1,2,3,3,3-heptafluoropropane (HFA 227).

Preferably, the aerosol formulation further comprises ethanol as a solvent.

For inhalation, the formulations of the present invention may be delivered via any inhalation methods known to those skilled in the art. Such inhalation methods and devices include, but are not limited to, metered dose inhalers with propellants such as CFC or HFA or propellants that are physiologically and environmentally acceptable. Other included devices are breath-operated inhalers, multidose dry powder inhalers and aerosol nebulizers. One preferred way of administering the formulations of the invention is by using conventional actuators. The term "actuator" as used in the present invention includes all types of actuators presently available including but not limited to standard metered dose inhalers or breath operated inhalers. Breath-actuated devices are also known, and have been the subject of many patent applications. Thus, for example, GB 1288971; GB 1297993; GB 1335378; GB 1383761; GB 1392192; GB 1413285; WO85/01880; GB 2204799; U.S. Pat. No. 4,803,978 and EP 0186280A describe inhalation-actuated dispensing devices for use with a pressurized aerosol-dispensing container.

In a preferred embodiment of the invention, administration is effected by a means of a pump or squeeze-actuated nebulizer. In more preferred embodiments of the invention administration is effected by means of a metered dose inhaler or an aerosol dispenser.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, caplets, gelcaps, cachets, pills, or tablets each containing a predetermined amount of the active ingredient as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil emulsion and as a bolus, etc. In a more preferred embodiment, administration is effected by liquid solutions, suspensions or elixirs, powders, lozenges, 10 micronized particles and osmotic delivery systems.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, the active ingredients in a free flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface active or dispersing agent. Molded tablets may be made by molding, in a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may be optionally coated or scored and may 20 be formulated to provide a slow or controlled release of the active ingredient therein.

Formulations of the present invention may conveniently be present in unit dosage form and may be prepared by conventional pharmaceutical techniques as discussed above. Such techniques include the step of bringing into association the Δ^8 THC moiety and the pharmaceutical carrier(s) or excipient(s). In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if 30 necessary, shaping the product.

Formulations suitable for administration by inhalation includes formulations of Δ^8 THC, in a form that can be dispensed by such inhalation devices known to those in the art. Such formulations may include carriers such as powders and

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aerosols. The inhalant compositions used in the present invention may comprise liquid or powdered compositions containing the active ingredient that are suitable for nebulization and intrabronchial use, or aerosol compositions administered via an aerosol unit dispensing metered doses.

Aerosol formulations for use in the subject method would typically include in addition to a therapeutically effective amount of a Δ^8 THC moiety and at least one propellant. The formulations of the inventions may be solutions or suspensions of the Δ^8 THC moieties.

Those of skill will appreciate that the amount of the Δ^8 THC moiety may be tailored based on the solubility of the active ingredients, stability, commercial necessities, and medical requirements. Preferred formulations comprise from about 0.01 to about 10% of Δ^8 THC moiety. More preferred formulations include from about 0.05 to about 6 %. Δ^8 THC moieties according to both aspects of the invention have been prepared from natural CBD by cyclization and purified by chromatography (see e.g., Abrahamov et al, *supra*). Preferably the Δ^8 THC moiety is synthesized to a acceptable pharmaceutical purity (greater than 99% pure).

Preferred propellants include hydrofluoroalkanes (HFAs; e.g., HFA 134a, HFA 227, or a blend thereof) or chlorofluorocarbons (CFCs).

In some embodiments, the formulation includes additional active components such as, for example, another cannabinoid. In particularly preferred embodiments, the additional cannabinoid is cannabidiol (CBD). CBD is commercially available. Optionally, the formulations may contain surfactants and co-solvents and may be filled into conventional aerosol containers that are closed by a suitable metering valve. In a particularly preferred embodiment, the formulation may include ethanol.

The following non-limiting examples of formulations are

representative for the purposes of illustration only:

Δ^8 THC moiety % (w/w)	CBD % (w/w)	Ethanol % (w/w)	HFA 134a % (w/w)	HFA 227 % (w/w)
0.02	0	0	99.98	0
0.02	0	2.0	0	97.98
0.05	0.05	0	99.9	0
1.0	0.5	10.0	48.5	40.0

The formulations according to the invention may optionally include any of the well known pharmaceutically acceptable carriers including diluents and excipients (see Remington's Pharmaceutical Sciences, 18th Ed., Gennaro, Mack Publishing Co., Easton, PA (1990) and Remington: The Science and Practice of Pharmacy, Lippincott, Williams & Wilkins (1995)).

Suitable liquid compositions comprise the active ingredient in an aqueous, pharmaceutically acceptable inhalant solvent, e.g., isotonic saline or bacteriostatic water. The solutions are administered by means of a pump or squeeze-activated nebulized spray dispenser, or by any other conventional means for causing or enabling the requisite dosage amount of the liquid composition to be inhaled into the patient's lungs.

Suitable powder compositions include, by way of illustration; powdered preparations of the active ingredient thoroughly intermixed with lactose or other inert powders acceptable for intrabronchial administration. The powder compositions can be administered via a dispenser, including but not limited to, an aerosol dispenser or encased in a breakable capsule which may be inserted by the patient into a device that punctures the capsule and blows the powder out in a steady stream suitable for inhalation.

Formulations suitable for topical administration in the mouth include lozenges comprising the ingredients in a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as 5 gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the ingredient to be administered in a suitable liquid carrier.

Formulations suitable for topical administration to the skin may be presented as ointments, creams, gels, lotions, and 10 pastes comprising the ingredient to be administered in a pharmaceutical acceptable carrier. A preferred topical delivery system is a transdermal patch containing the ingredient to be administered.

Formulations for rectal administration may be prepared as 15 a suppository with a suitable base comprising, such as, for example, cocoa butter.

Formulations for nasal administration, wherein the carrier is a solid, include a coarse powder having a particle size, for example, in the range of 20 to 500 microns which is 20 administered in the manner in which snuff is administered, i.e., by rapid inhalation through the nasal passage from a container of the powder held close up to the nose. Suitable formulations wherein the carrier is a liquid, for administration for example via a nasal spray, aerosol, or as 25 nasal drops, include aqueous or oily solutions of the active ingredient.

Formulations suitable for vaginal administration may be presented as pessaries, suppositories, tampons, creams, gels, pastes, foams or spray formulations containing, in addition to 30 the active ingredients, such carriers as are known in the art to be appropriate.

Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain antioxidants, stabilizers, buffers, bacteriostats, and

solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or 5 multi-dose containers, for example, sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) conditions requiring only the addition of the sterile liquid carrier, for example, water for injections, immediately prior to use.

Extemporaneous injection solutions and suspensions may be 10 prepared from sterile powders, granules, and tablets of the kind previously described.

In a second aspect, the invention provides methods for treating a mammal to alleviate the symptoms associated with a number of disease states. Therefore, an object of the invention 15 is (a) the reduction, elimination or prevention of pain associated with any medical condition; (b) the stimulation of appetite; (c) the reduction, elimination or prevention of nausea; (d) the reduction, elimination or prevention of vomiting (anti-emetic properties); (e) the relaxation of muscle 20 tissue (e.g., for the treatment of multiple sclerosis).

The term "mammal" is used to designate any warm-blooded animal. Accordingly, the invention is useful for medical as well as veterinary uses.

The formulations used are as described for the first 25 aspect of the invention. Therapeutically effective amounts of the formulations are administered to mammals potentially benefiting from treatment with a Δ^8 THC moiety for a therapeutically effective period of time. Dosages will depend on the condition being treated, the particular compound, and 30 other clinical factors such as weight and condition of the mammal and the route of administration.

The term "therapeutically effective amount" and "therapeutically effective period of time" are used to denote treatments at dosages and for periods effective to achieve the

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therapeutic result sought. Furthermore, one of skill will appreciate that the therapeutically effective amount of Δ^8 THC moiety may be lowered or increased by fine tuning and altering the amount of the other component. The invention therefore provides a method to tailor the administration/ treatment to the particular exigencies specific to a given mammal. Therapeutically effective ranges may be easily determined for example empirically by starting at relatively low amounts and by step-wise increments with concurrent evaluation of inhibition.

EXAMPLES

Example I

To identify dose-limiting toxicity, healthy human volunteers are administered Δ^8 Tetrahydrocannabinol aerosol formulations according to the invention at low dosages which are incrementally escalated while monitoring the subjects for dose-limiting side effects (such as psychotropic symptoms).

Example II

To identify therapeutically effective amounts and times, terminal oncology patients are administered Δ^8 Tetrahydrocannabinol aerosol formulations according to the invention at low dosages which are incrementally escalated until either the maximum acceptable level in Example I is reached, or the side effects in patients become too high, or sufficient efficacy is seen that increasing the dose further is unnecessary.

The following examples illustrate alternative aerosol formulations.

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Example 1

Ingredient	Weight in g
Ethanol	0.10
5 P-134a	2.02
delta-8-THC	0.01
Lipoid S100 TM	0.05

Lipoid S100TM is a phospholipid.

10

Example 2

Ingredient	Weight in g
Ethanol	0.09
15 P-134a	1.83
delta-8-THC	0.01
Brij TM	0.02

BrijTM is a Lauryl Polyoxyethylene

20

Example 3

Ingredient	Weight in g
Ethanol	0.20
25 P-134a	3.80
delta-8-THC	0.01
Salbutamol Sulphate	0.01

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Claims

1. Use of Δ^8 Tetrahydrocannabinol in the manufacture of an aerosol formulation for medicinal administration to a patient from an aerosol delivery device.
2. Use as claimed in claim 1, in which the patient is suffering from a condition selected from pain, nausea, vomiting, appetite loss, multiple sclerosis and asthma.
3. Use as claimed in claim 2, in which the patient is a cancer patient undergoing chemotherapy, and the condition is selected from pain, nausea, vomiting and appetite loss.
4. Use as claimed in claim 2, in which the condition is pain associated with phantom limb syndrome.
5. Use as claimed in claim 2, in which the condition is appetite loss associated with anorexia nervosa.
6. Use as claimed in any one of claims 1 to 5, in which the aerosol formulation is for administration to the lungs of the patient.
7. Use as claimed in any one of claims 1 to 5, in which the aerosol formulation is for administration to the buccal or nasal mucosa of the patient.
8. Use of Δ^8 Tetrahydrocannabinol in the manufacture of a medicament for the treatment of a condition selected from pain, appetite loss, multiple sclerosis and asthma.

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9. An aerosol delivery device containing an aerosol formulation comprising Δ^8 Tetrahydrocannabinol.
10. A device as claimed in claim 9, which is a metered dose inhaler and in which the aerosol formulation further comprises a propellant.
5
11. A device as claimed in claim 10, in which the propellant is selected from 1,1,1,2-tetrafluoroethane and 1,1,1,2,3,3-heptafluoropropane.
10
12. A device as claimed in claim 10 or claim 11, in which the aerosol formulation further comprises ethanol as a solvent.
13. An aerosol formulation for use in an aerosol delivery device, which comprises Δ^8 Tetrahydrocannabinol.
15
14. An aerosol formulation as claimed in claim 13, which further comprises a propellant.
15. An aerosol formulation as claimed in claim 14, in which the propellant is selected from 1,1,1,2-tetrafluoroethane and 1,1,1,2,3,3-heptafluoropropane.
20
16. An aerosol formulation as claimed in claim 14 or claim 15, which further comprises ethanol as a solvent.
25
17. A method of treating a mammal suffering from a condition indicating treatment with a Δ^8 Tetrahydrocannabinol, which comprises administering an aerosolized aerosol formulation containing a therapeutically effective amount of Δ^8 Tetrahydrocannabinol to the mammal.
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18. A method as claimed in claim 17, in which the mammal is suffering from a condition selected from pain, nausea, vomiting, appetite loss, multiple sclerosis and asthma.
- 5 19. A method as claimed in claim 18, in which the mammal is a cancer patient undergoing chemotherapy, and the condition is selected from pain, nausea, vomiting and appetite loss.
- 10 20. A method as claimed in claim 18, in which the condition is pain associated with phantom limb syndrome.
21. A method as claimed in claim 18, in which the condition is appetite loss associated with anorexia nervosa.
- 15 22. A method as claimed in claim 17, in which the aerosolized aerosol formulation is administered to the lungs of the mammal.
- 20 23. A method as claimed in claim 17, in which the aerosolized aerosol formulation is administered to the buccal or nasal mucosa of the mammal.
24. A method of treating a mammal suffering from a condition selected from pain, appetite loss, multiple sclerosis and asthma, which comprises administering a therapeutically effective amount of Δ^8 Tetrahydrocannabinol to the mammal.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 02/03161

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/352 A61K9/12 A61P1/08 A61P3/04 A61P11/06
A61P21/04 A61P29/02 A61K9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, MEDLINE, PASCAL, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01 03668 A (SHEK PANG N ;ZAMECNIK JIRI (CA); HUNG ORLANDO (CA); TIKUISIS PETER) 18 January 2001 (2001-01-18) claims 6,24; example 15 ---	8,24
X	WO 99 32107 A (DAVIS STANLEY STEWART ;WATTS PETER JAMES (GB); DANBIOSYST UK (GB)) 1 July 1999 (1999-07-01) page 3, line 22-29; claim 18 ---	8,24 -/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

20 September 2002

Date of mailing of the International search report

30/09/2002

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INTERNATIONAL SEARCH REPORT

Int'l Application No
PCT/GB 02/03161

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	TASHKIN D P ET AL: "BRONCHIAL EFFECTS OF ORAL CANNABINOIDS IN HEALTHY AND ASTHMATIC SUBJECTS" ANNUAL MEETING AMERICAN LUNG ASSOCIATION IN CONJUNCTION WITH ANNUAL MEETING AMERICAN THORACIC SOCIETY AND ANNUAL MEETING OF CONGRESS OF LUNG ASSOCIATION STAFF, XX, XX, vol. 119, no. 4, 13 May 1979 (1979-05-13), page 82 XP002114268 abstract ---	8,24
X	WO 00 24362 A (UNIV VIRGINIA COMMONWEALTH) 4 May 2000 (2000-05-04) claims 1-23; table 3 ---	1-7,9-23
A	WO 93 05031 A (VISSUM RES DEV CO) 18 March 1993 (1993-03-18) the whole document ---	1-24
A	US 5 605 928 A (MECHOULAM RAPHAEL ET AL) 25 February 1997 (1997-02-25) cited in the application the whole document ---	1-24

INTERNATIONAL SEARCH REPORT

ational application No.
PCT/GB 02/03161

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Rule 39.1(iv) PCT – Method for treatment of the human or animal body by therapy Although claims 17–24 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

In
International Application No
PCT/GB 02/03161

Patent document cited in search report		Publication date		Patent family member(s)	Publication date
WO 0103668	A	18-01-2001	AU WO EP	5958200 A 0103668 A1 1109533 A1	30-01-2001 18-01-2001 27-06-2001
WO 9932107	A	01-07-1999	AU CA EP WO JP NO NZ US ZA	1497299 A 2313316 A1 1039898 A1 9932107 A1 2001526221 T 20003161 A 504679 A 6383513 B1 9811528 A	12-07-1999 01-07-1999 04-10-2000 01-07-1999 18-12-2001 16-06-2000 28-06-2002 07-05-2002 12-10-2000
WO 0024362	A	04-05-2000	AU BR CN EP WO US	2143000 A 9915095 A 1324236 T 1124551 A2 0024362 A2 2002031480 A1	15-05-2000 15-01-2002 28-11-2001 22-08-2001 04-05-2000 14-03-2002
WO 9305031	A	18-03-1993	IL AT AU AU CA DE DE EP JP JP WO US US	99468 A 187721 T 664204 B2 2678792 A 2118929 A1 69230446 D1 69230446 T2 0642504 A1 3298881 B2 7505119 T 9305031 A1 5635530 A 5538993 A	30-09-1997 15-01-2000 09-11-1995 05-04-1993 18-03-1993 20-01-2000 13-04-2000 15-03-1995 08-07-2002 08-06-1995 18-03-1993 03-06-1997 23-07-1996
US 5605928	A	25-02-1997	IL JP AU CA CZ WO HU	102082 A 8500336 T 4318793 A 2136977 A1 9402907 A3 9324125 A1 70213 A2	13-07-1997 16-01-1996 30-12-1993 09-12-1993 15-03-1995 09-12-1993 28-09-1995